REMARKS

Applicants have studied the Office Action, and have amended the claims in response thereto. It is respectfully submitted that the application, as amended, is in condition for allowance. Claims 185-210 are pending in the present application. Claims 185-187, 189-191, 200 and 202 have been rejected; claims 188 and 192 have been objected to (although Examiner had indicated that these claims would be allowable if rewritten in independent form and incorporating all of the limitations of their respective base claims and any intervening claims); and claim 201 was indicated as allowable. Applicants thank Examiner for allowing claim 201, and indicating that claims 188 and 192 would be allowable if rewritten in independent form. Claims 195 and 198-200 have been amended, and claims 203-210 have been added. No new matter has been added. Reconsideration and allowance of the claims in view of the foregoing amendment and the ensuing remarks are respectfully requested.

Claim 185 has been amended to more particularly describe that which Applicants consider to be their invention. As amended, claim 185 describes an HSV-1-derived vector that does not reactivate from latency. Support for this amendment may be found throughout the specification; for example, at page 9, lines 26-28.

Claim 195 has been amended to more particularly describe that which Applicants consider to be their invention. As amended, claim 195 describes a mammalian cell containing an HSV-1-derived vector, wherein the cell is a non-human mammalian cell, an isolated mammalian cell, or a non-human isolated mammalian cell. Moreover, the HSV-1-derived vector does not reactivate from latency. Support for this amendment may be found throughout the specification and claims as originally presented in Applicants' preliminary amendment of October 29, 2001; for example, at page 16, lines 21-25 and at page 9, lines 26-28 of the specification.

Claims 198 and 199 have been amended to more particularly describe that which Applicants consider to be their invention. As amended, claims 198 and 199 each describe sources from which the mammalian cell of the invention has been derived, and no longer include embodiments of the present invention wherein the mammalian cell is contained in any particular tumor or mammal.

Claim 200 has been amended to more particularly describe that which Applicants

consider to be their invention. As amended, claim 200 describes a mammalian cell containing an HSV-1-derived vector, wherein the cell is a non-human mammalian cell, an isolated mammalian cell, or a non-human isolated mammalian cell. Support for this amendment may be found throughout the specification and claims as originally filed; for example, at page 16, lines 21-25 of the specification.

New claims 203-207 describe a non-human mammal containing the mammalian cell described in claims 195-199 of the present invention. This embodiment of the present invention is now described in a separate set of claims that more clearly sets forth the metes and bounds of the present invention. Support for these claims may be found in the specification and claims as originally presented in Applicants' preliminary amendment of October 29, 2001; for example, at page 11, lines 21-23.

New claims 208-210 describe an HSV-1-derived vector selected from PromΔLATΔ34.5, PromΔLATΔ34.5-GFP, and derivatives of either. Support for this amendment may be found throughout the specification; for example, at page 15, line 10 through page 16, line 20.

Examiner indicated that the declaration filed with the present application is defective and required the submission of a new oath or declaration in compliance with 37 CFR 1.67(a). In particular, Examiner noted that the declaration *"does not identify the citizenship of inventor Anthony B. Nesburn."*

Applicants enclose herewith a supplemental declaration, which includes an indication of inventor Anthony B. Nesburn's citizenship as well as an identification of the entire inventive entity. 37 CFR 1.67(a). The supplemental declaration is signed by Anthony B. Nesburn. Id. Moreover, this supplemental declaration specifically references the parent application to the present divisional application (*i.e.*, U.S. patent application serial No. 09/299,817, filed April 26, 1999). Id. Applicants believe that this supplemental declaration satisfies the requirements of 37 CFR 1.67(a).

Examiner indicated that reference number 35 (*i.e.*, Huard, J. *et al.*) of the information disclosure statement filed on October 29, 2001 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it does not provide a date for this reference.

Applicants enclose herewith an information disclosure statement, as well as a corresponding form PTO-1449 properly listing the Huard *et al.* reference originally described in the information disclosure statement of October 29, 2001. The fee required under 37 CFR 1.17(p) is also enclosed. Applicants thus respectfully submit that this information disclosure statement and the Huard *et al.* reference described therein must be considered. 37 CFR 1.97(c), MPEP § 609.

Examiner rejected claims 195-200 under 35 U.S.C. § 101, as being directed to non-statutory subject matter. In particular, Examiner found that the claims describe mammalian cells that contain an HSV-1 derived vector. Moreover, *"[c]laim 199, which depends on claim 195, recites wherein the cell is contained in a human."* Examiner noted that *"[c]laims which read on cells present in a human encompass the human being,"* and that *"[h]umans are non-statutory subject matter."* Examiner further suggested that Applicants amend claim 195 to describe either a *"non-human mammalian cell,"* or *"an isolated mammalian cell,"* and to amend claim 199 accordingly. This rejection is respectfully traversed.

Per Examiner's suggestion, Applicants have amended claims 195 and 200 to describe mammalian cells that are limited to non-human mammalian cells, isolated mammalian cells, and non-human isolated mammalian cells. Thus, the claims do not include mammalian cells that can be said to encompass a human being.

In light of the foregoing remarks, Applicants respectfully submit that claims 195 (from which claims 196-199 depend) and 200 are directed to statutory subject matter. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 101.

Examiner rejected claims 195-200 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out that which Applicants regard as their invention. In particular, Examiner noted that *"it is unclear whether the applicant intends to claim isolated cells or isolated tumor containing the cells, or whether the applicant intends to claim humans or other types of mammals which comprise these cells or tumors."* Examiner therefore concluded that *"the claims are confusing and the metes and bounds of the claims cannot be determined."* This rejection is respectfully traversed.

Claims 198 and 199, both of which depend from claim 195, have been amended to describe sources from which the mammalian cell of the invention has been *derived*, and no longer include embodiments of the present invention wherein the mammalian cell is *contained* in any particular tumor or mammal. Thus, claim 195 is limited to a mammalian cell that may be derived from various types of tumor (*i.e.*, claim 198) and/or mammal (*i.e.*, claim 199).

With respect to claim 200, Examiner indicated that this claim depends from claim 195, however Applicants respectfully point out that this is not the case. In fact, claim 200 multiply depends from claims 185, 186, 187, 189, 190, 191, 193, or 194. As such, Applicants believe that this rejection is improper with respect to claim 200.

In light of the foregoing remarks, Applicants respectfully submit that claims 195 (from which claims 196-199 depend) and 200 are sufficiently definite and their metes and bounds can be readily ascertained. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Examiner rejected claims 185-187, 189, 195-197, 199-200 and 202 under 35 U.S.C. § 103(a) as being rendered obvious by Efstathiou *et al.* (U.S. Patent No. 6,193,980 B1; "Efstathiou") in view of Roizman *et al.* (U.S. Patent No. 6,340,673 B1; "Roizman"). In particular, Examiner found that Efstathiou *"teaches recombinant HSV-1 vectors and viruses in which an heterologous DNA is operatively linked to the LAT promoter, thus introducing a deletion into the LAT region such that normal LAT transcripts are not detected,"* but that *"[Efstathiou] differs from the instant invention by failing to specifically teach that the HSV vector further lacks the ICP34.5 gene product due to a deletion in both copies of the ICP34.5 gene."* Examiner further found that *"[Roizman] supplements [Efstathiou] by teaching that the deletion of both copies of the ICP 34.5 gene in an HSV virus result in an attenuated virus designated R3616 with reduced neurovirulence."* Examiner concluded that *"based on the teachings of [Efstathiou] that it is preferable that the HSV vectors encoding a heterologous gene operatively linked to the LAT promoter be replication defective and/or attenuated, and the teachings of [Roizman] that an HSV virus having a deletion in both copies of the ICP 34.5 gene is among the least pathogenic of known HSV viruses, it would have been* prima facie *obvious to the skilled artisan to introduce the heterologous gene into the LAT region of the R3616 virus in*

order to generate an HSV which has decreased neurovirulence and which is capable of expressing the heterologous protein for extended periods of time." Examiner additionally noted that *"based on high degree of skill in the art of molecular biology at the time of filing and the detailed directions provided by both [Roizman] and [Efstathiou] for modifying the genome of the HSV virus, the skilled artisan would have had a reasonable expectation of success in making and using the HSV vector which has a deletion in the LAT region, a heterologous gene operatively linked to the LAT promoter, and a deletion in the ICP 34.5 gene."* This rejection is respectfully traversed.

Three basic criteria must be met to establish a *prima facie* case of obviousness: (1) *"there must be some suggestion or motivation . . . to combine reference teachings,"* (2) *"there must be a reasonable expectation of success,"* and (3) the prior art references *"must teach or suggest all the claim limitations."* MPEP § 2142 (emphasis added). Moreover, *"[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure."* Id. (citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); emphasis added).

First, Efstathiou in view of Roizman does not teach, disclose or suggest all of the limitations of Applicants' claims. As amended, each of Applicants' independent claims that were rejected by Examiner in this section relate to an HSV-1-derived vector that *does not reactivate from latency*. In marked contrast, the recombinant HSV-1-derived vectors of Efstathiou and the ICP34.5 -/- HSV vectors of Roizman *do* reactivate from latency to an appreciable degree. With respect to Roizman, this is addressed in the following passage from Applicants' specification:

> Roizman described a recombinant, purportedly avirulent HSV lacking the ability to express a functional γ34.5 gene product, a neurovirulence factor. (Roizman, *Recombinant Herpes Simplex Viruses vaccines and methods*, U.S. Patent No. 5,328,688). Spontaneous reactivation rates of these mutants was only relatively attenuated, not entirely eliminated. (E.g., G.-C. Perng *et al.*, J. Virol. 70(5):2883-93 [1996]; G.-C. Perng *et al.*, J. Virol. 69(5):3033-411 [1995]). [*See* Specification, p.3, line 28 through p.4, line 3; emphasis added]

As such, the prior art references do not describe each limitation of Applicants' claims, as amended. The references describe only the features of the LAT null mutants and the γ34.5 null

mutants -- *not* the surprising synergistic features of an HSV-1-derived vector that combines these features. That the Applicants' HSV-1-derived vectors do not reactivate from latency is significant, and is described repeatedly throughout their specification. For example, Applicants note that *"[o]ne of the advantages of using a combined LAT null mutant and γ34.5 null mutant HSV-1-derived vector, compared to LAT null mutants or γ34.5 null mutants, is that regardless of the infectious dose, the double mutant does not reactivate from latency."* *See* Specification, p.9, lines 26-28 (emphasis added). This aspect of Applicants' invention is not suggested by Efstathiou in view of Roizman; at most, these references suggest a somewhat attenuated HSV-1-derived vector, but not one in which the vector does not reactivate from latency.

Second, neither Efstathiou nor Roizman teaches, discloses or suggests that the combination of their teachings would be desirable. There were numerous null mutant HSV-1-derived vectors known in the art at the time of filing the present application, including the single null mutant HSV-1-derived vectors described in each of Efstathiou and Roizman. However, there is no suggestion in either of these references that their combination would be particularly beneficial. Furthermore, there is no indication in either of these references that the inventive HSV-1-derived vectors would exhibit a substantial inability to reactivate from latency, and, thus, there can be no reasonable expectation of success in achieving this feature in the references themselves. In fact, the only reference that appears to suggest that a double mutant would exhibit this property is the present application. However, as noted above, the suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and can not be based on Applicants' disclosure.

In light of the foregoing remarks, Applicants respectfully submit that claims 185-187, 189, 195-197, 199-200 and 202 are not rendered obvious by Efstathiou in view of Roizmann. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

Examiner rejected claims 190, 191, 193 and 194 under 35 U.S.C. § 103(a) as being rendered obvious by Efstathiou in view of Roizman and further in view of Coffin *et al.* (WO 98/047126; "Coffin"). In particular, Examiner found that Coffin *"supplements the teachings of [Efstathiou] and [Roizman] by teaching HSV vectors wherein the LAT promoter can be used to express a variety of cytokines and immune effector molecules including interferon-gamma and*

tumor necrosis factor." Based on this, Examiner concluded that *"provided the motivation for expressing cytokines using the LAT promoter in an HSV vector as taught by [Coffin], it would have been* prima facie *obvious to the skilled artisan to utilize a cytokine gene such as interferon-gamma or tumor necrosis factor as the therapeutic gene in the HSV vectors taught by [Efstathiou] in view of [Roizman]."* Examiner further noted that *"based on the detailed instructions of modifying HSV vectors as provided by [Efstathiou], [Roizman], and [Coffin], the skilled artisan would have had a reasonable expectation of success."* This rejection is respectfully traversed.

For the reasons set forth above, it is respectfully submitted that Efstathiou in view of Roizman does not render obvious Applicants' invention, as claimed. These references do not describe each feature of Applicants' invention, there is no suggestion or motivation therein to combine their teachings and there is no reasonable expectation of success in the references themselves. As such, it is respectfully submitted that the further combination of these references with Coffin fails to render Applicants' claimed invention obvious.

In light of the foregoing remarks, Applicants respectfully submit that claims 191, 192, 193 and 194 are not rendered obvious by Efstathiou in view of Roizmann in further view of Coffin. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

Examiner rejected claim 191 under 35 U.S.C. § 103(a) as being rendered obvious by Efstathiou in view of Roizman and further in view of Ho *et al.* (Mol. Brain. Res., vol. 41 (1-2), 200-209 (1996); "Ho"). In particular, Examiner found that Ho *"supplements the teachings of [Efstathiou] and [Roizman] by teaching various reporter genes which can be used to test the activity of promoters in HSV vectors."* Examiner noted that Ho describes luciferase as being *"equally efficient as lacZ as a reported gene in HSV vectors"* and thus concluded that *"it would have been* prima facie *obvious to the skilled artisan at the time of filing to use either lacZ or luciferase as a reporter gene in HSV vectors."* Examiner further noted that *"based on the high level of skill in molecular biology and the detailed instructions for modifying HSV vectors provided by [Efstathiou], [Roizman] and [Ho], the skilled artisan would have had a reasonable expectation of success in replacing the lacZ gene taught by [Efstathiou] with the luciferase gene*

taught by [Ho]." This rejection is respectfully traversed.

For the reasons set forth above, it is respectfully submitted that Efstathiou in view of Roizman does not render obvious Applicants' invention, as claimed. These references do not describe each feature of Applicants' invention, there is no suggestion or motivation therein to combine their teachings and there is no reasonable expectation of success in the references themselves. As such, it is respectfully submitted that the further combination of these references with Ho fails to render Applicants' claimed invention obvious.

In light of the foregoing remarks, Applicants respectfully submit that claim 191 is not rendered obvious by Efstathiou in view of Roizmann in further view of Ho. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

Applicants also note that new counsel has been appointed to prosecute the present application. As such, and by virtue of the *Power of Attorney from Assignee and Revocation of Prior Powers* being submitted herewith, please direct all future correspondence in this matter to:

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Applicants believe that the present amendment and foregoing remarks place the application in condition for allowance. A favorable action is respectfully requested. If for any reason Examiner finds the application other than in condition for allowance, Examiner is

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requested to call the undersigned attorney at the Los Angeles telephone number (213) 488-7100 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
PILLSBURY WINTHROP LLP

Date: March 12, 2004

By: _____

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